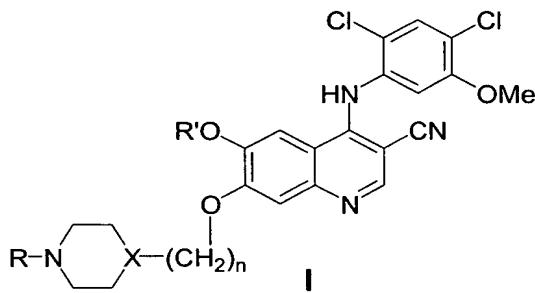


What is claimed:

1. A method of providing neuroprotection in a patient following a cerebrovascular ischemic event comprising providing a therapeutically effective amount of a compound of the formula



wherein:

X is N, CH

n is an integer from 1-3; and

10 R' and R are independently, alkyl of 1 to 3 carbon atoms, and pharmaceutically acceptable salts thereof; with the proviso that when n is 1, X is not N.

2. The method of Claim 1 wherein R' is methyl.

15 3. The method of Claim 1 wherein R is methyl or ethyl.

4. The method of Claim 1 wherein X is N.

5. The method of Claim 1 wherein X is CH.

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6. The method of Claim 1 wherein the compound is:

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 7-[3-(4-ethyl-1-piperazinyl)propoxy]- 6-

25 methoxy-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[2-(4-methyl-1-piperazinyl)ethoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 7-[2-(4-ethyl-1-piperazinyl)ethoxy]- 6-methoxy-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]-3-quinolinecarbonitrile;

5 4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-[(1-ethylpiperidin-4-yl)methoxy]-6-

10 methoxyquinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile;

15 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-ethylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(4-methyl-1-

20 piperazinyl)ethoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]quinoline-3-carbonitrile; or

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[3-(4-propyl-1-

25 piperazinyl)propoxy]-3-quinolinecarbonitrile; and pharmaceutically acceptable salts thereof.

7. The method of Claim 1 wherein compound is administered between about 6 to about 24 hours after the ischemic event.

30 8. The method of Claim 1 wherein the therapeutically effective amount is from about 1 mg/kg to about 30 mg/kg.

9. The method of Claim 1 comprising administering compound of Formula I intravenously.

10. The method of Claim 1 wherein the patient is a human.

5

11. The method of Claim 1 wherein the ischemic event is transient.

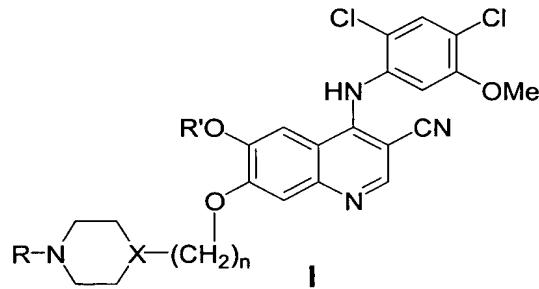
12. The method of Claim 1 wherein the ischemic event is acute.

10 13. The method of Claim 1 wherein the ischemic event is stroke, head trauma, spinal trauma, general anoxia, or hypoxia.

14. The method of Claim 1 wherein the ischemic event occurs during cranial hemorrhage, perinatal asphyxia, cardiac arrest or status epilepticus.

15

15. A method of inhibiting neurological deficits in a patient following a cerebrovascular ischemic event comprising providing a therapeutically effective amount of a compound of the formula



20 wherein:

X is N, CH

n is an integer from 1-3; and

R' and R are independently, alkyl of 1 to 3 carbon atoms, and pharmaceutically acceptable salts thereof; with the proviso that when n is 1, X is not N.

25

16. The method of Claim 15 wherein R' is methyl.

17. The method of Claim 15 wherein R is methyl or ethyl.

18. The method of Claim 15 wherein X is N.

19. The method of Claim 15 wherein X is CH.

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20. The method of Claim 15 wherein the compound is:

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile;  
4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 7-[3-(4-ethyl-1-piperazinyl)propoxy]- 6-methoxy-3-quinolinecarbonitrile;  
4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[2-(4-methyl-1-piperazinyl)ethoxy]-3-quinolinecarbonitrile;  
4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 7-[2-(4-ethyl-1-piperazinyl)ethoxy]- 6-methoxy-3-quinolinecarbonitrile;  
15 4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]-3-quinolinecarbonitrile;  
4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]-3-quinolinecarbonitrile;  
4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;  
20 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-[(1-ethylpiperidin-4-yl)methoxy]-6-methoxyquinoline-3-carbonitrile;  
4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile;  
25 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile;  
4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-ethylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile;  
4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;  
30 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(4-methyl-1-piperazinyl)ethoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]quinoline-3-carbonitrile; or

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-propyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile; and pharmaceutically acceptable salts

5 thereof.

21. The method of Claim 15 wherein compound is administered between about 6 to about 24 hours after the ischemic event.

10 22. The method of Claim 15 wherein the therapeutically effective amount is from about 1 mg/kg to about 30 mg/kg.

23. The method of Claim 15 comprising administering compound of Formula I intravenously.

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24. The method of Claim 15 wherein the patient is a human.

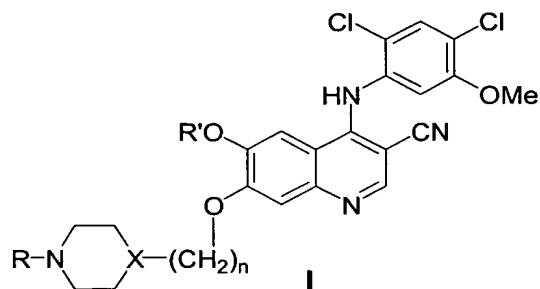
25. The method of Claim 15 wherein the ischemic event is transient.

20 26. The method of Claim 15 wherein the ischemic event is acute.

27. The method of Claim 15 wherein the ischemic event is stroke, head trauma, spinal trauma, general anoxia, or hypoxia.

25 28. The method of Claim 15 wherein the ischemic event occurs during cranial hemorrhage, perinatal asphyxia, cardiac arrest or status epilepticus.

29. A method of reducing infarct volumes in a patient following a cerebrovascular ischemic event comprising administering a therapeutically effective amount of a 30 compound of the formula



wherein:

X is N, CH

n is an integer from 1-3; and

5 R' and R are independently, alkyl of 1 to 3 carbon atoms, and pharmaceutically acceptable salts thereof; with the proviso that when n is 1, X is not N.

30. The method of Claim 29 wherein R' is methyl.

10 31. The method of Claim 29 wherein R is methyl or ethyl.

32. The method of Claim 29 wherein X is N.

33. The method of Claim 29 wherein X is CH.

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34. The method of Claim 29 wherein the compound is:

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile;

20 4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 7-[3-(4-ethyl-1-piperazinyl)propoxy]- 6-methoxy-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[2-(4-methyl-1-piperazinyl)ethoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 7-[2-(4-ethyl-1-piperazinyl)ethoxy]- 6-methoxy-3-quinolinecarbonitrile;

25 4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-[(1-ethylpiperidin-4-yl)methoxy]-6-methoxyquinoline-3-carbonitrile;

5 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-ethylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile;

10 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(4-methyl-1-piperazinyl)ethoxy]quinoline-3-carbonitrile;

15 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]quinoline-3-carbonitrile; or

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(4-propyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile; and pharmaceutically acceptable salts thereof.

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35. The method of Claim 29 wherein compound is administered between about 6 to about 24 hours after the ischemic event.

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36. The method of Claim 29 wherein the therapeutically effective amount is from about 1 mg/kg to about 30 mg/kg.

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37. The method of Claim 29 comprising administering compound of Formula I intravenously.

38. The method of Claim 29 wherein the patient is a human.

39. The method of Claim 29 wherein the ischemic event is transient.

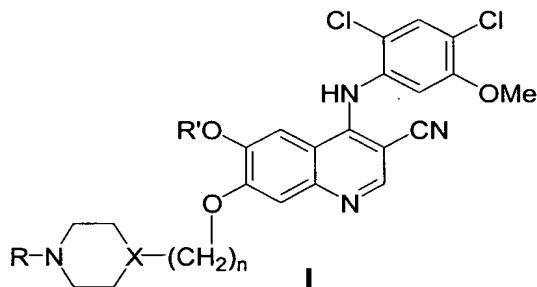
40. The method of Claim 29 wherein the ischemic event is acute.

41. The method of Claim 29 wherein the ischemic event is stroke, head trauma, spinal trauma, general anoxia, or hypoxia.

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42. The method of Claim 29 wherein the ischemic event occurs during cranial hemorrhage, perinatal asphyxia, cardiac arrest or status epilepticus.

43. A method of inhibiting post-ischemic vascular permeability of cerebral blood vessels in a patient suffering from a cerebrovascular event comprising administering a therapeutically effective amount of a compound of the formula



wherein:

X is N, CH

15 n is an integer from 1-3; and

R' and R are independently, alkyl of 1 to 3 carbon atoms, and pharmaceutically acceptable salts thereof; with the proviso that when n is 1, X is not N.

44. The method of Claim 43 wherein R' is methyl.

20

45. The method of Claim 43 wherein R is methyl or ethyl.

46. The method of Claim 43 wherein X is N.

25 47. The method of Claim 43 wherein X is CH.

48. The method of Claim 43 wherein the compound is:

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 7-[3-(4-ethyl-1-piperazinyl)propoxy]- 6-methoxy-3-quinolinecarbonitrile;

5 4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[2-(4-methyl-1-piperazinyl)ethoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 7-[2-(4-ethyl-1-piperazinyl)ethoxy]- 6-methoxy-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]-3-quinolinecarbonitrile;

10 4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;

15 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-[(1-ethylpiperidin-4-yl)methoxy]-6-methoxyquinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile; 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-ethylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile;

20 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(4-methyl-1-piperazinyl)ethoxy]quinoline-3-carbonitrile;

25 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]quinoline-3-carbonitrile; or

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[3-(4-propyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile; and pharmaceutically acceptable salts thereof.

30

49. The method of Claim 43 wherein compound is administered between about 6 to about 24 hours after the ischemic event.

50. The method of Claim 43 wherein the therapeutically effective amount is from about 1 mg/kg to about 30 mg/kg.

5 51. The method of Claim 43 comprising administering compound of Formula I intravenously.

52. The method of Claim 43 wherein the patient is a human.

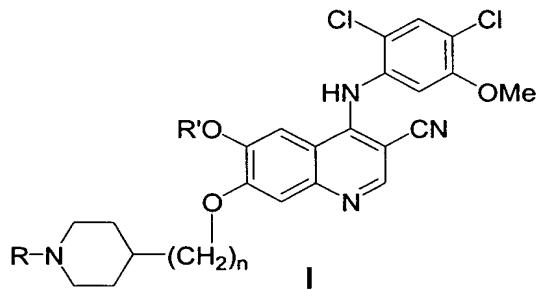
10 53. The method of Claim 43 wherein the ischemic event is transient.

54. The method of Claim 43 wherein the ischemic event is acute.

55. The method of Claim 43 wherein the ischemic event is stroke, head trauma, 15 spinal trauma, general anoxia, or hypoxia.

56. The method of Claim 43 wherein the ischemic event occurs during cranial hemorrhage, perinatal asphyxia, cardiac arrest or status epilepticus.

20 57. A compound having the structure:



wherein:

n is an integer from 1-3; and

25 R' and R are independently, alkyl of 1 to 3 carbon atoms, and pharmaceutically acceptable salts thereof.

58. A compound of Claim 57 wherein R' is methyl.

59. A compound of Claim 57 wherein R is methyl or ethyl.

60. A compound which is:

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-(1-methylpiperidin-4-yl)methoxy]-3-quinolinecarbonitrile;

5 4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;

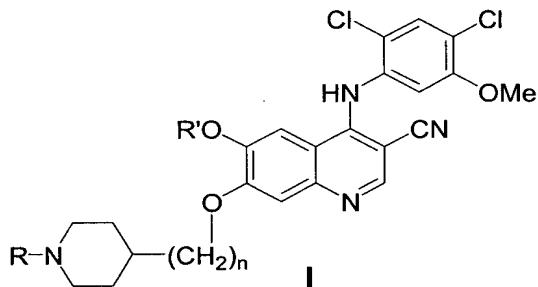
10 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-[(1-ethylpiperidin-4-yl)methoxy]-6-methoxyquinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-ethoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile;

15 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile; or

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]quinoline-3-carbonitrile; and pharmaceutically acceptable salts thereof.

20 61. A pharmaceutical composition comprising a compound having the structure



wherein:

n is an integer from 1-3; and

25 R' and R are independently, alkyl of 1 to 3 carbon atoms, and pharmaceutically acceptable salts thereof; and a pharmaceutically acceptable carrier or excipient.

62. A pharmaceutical composition of Claim 61 comprising a compound which is:

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-(1-methylpiperidin-4-yl)methoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]-3-quinolinecarbonitrile;

5 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-[(1-ethylpiperidin-4-yl)methoxy]-6-methoxyquinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-ethoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile;

10 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile; or

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]quinoline-3-carbonitrile; and pharmaceutically acceptable salts thereof.

15

63. A pharmaceutical composition comprising a vascular permeability inhibiting amount of a compound having the structure:

I

wherein:

20 X is N, CH

n is an integer from 1-3; and

R' and R are independently, alkyl of 1 to 3 carbon atoms, and pharmaceutically acceptable salts thereof, with the proviso that when n is 1, X is not N, and a pharmaceutical carrier or excipient.

25

64. A pharmaceutical composition of Claim 63 comprising a compound which is :

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[3-(4-methyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 7-[3-(4-ethyl-1-piperazinyl)propoxy]- 6-methoxy-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[2-(4-methyl-1-piperazinyl)ethoxy]-3-quinolinecarbonitrile;

5 4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 7-[2-(4-ethyl-1-piperazinyl)ethoxy]- 6-methoxy-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[(1-methylpiperidin-4-yl)methoxy]-3-quinolinecarbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]-3-quinolinecarbonitrile;

10 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-methoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-7-[(1-ethylpiperidin-4-yl)methoxy]-6-methoxyquinoline-3-carbonitrile;

15 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-methylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[(1-methylpiperidin-4-yl)methoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(4-ethylpiperazin-1-yl)propoxy]quinoline-3-carbonitrile;

20 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[3-(1-methylpiperidin-4-yl)propoxy]quinoline-3-carbonitrile;

4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(4-methyl-1-piperazinyl)ethoxy]quinoline-3-carbonitrile;

25 4-[(2,4-Dichloro-5-methoxyphenyl)amino]-6-ethoxy-7-[2-(1-methylpiperidin-4-yl)ethoxy]quinoline-3-carbonitrile; or

4-[(2,4-Dichloro-5-methoxyphenyl)amino]- 6-methoxy-7-[3-(4-propyl-1-piperazinyl)propoxy]-3-quinolinecarbonitrile; and pharmaceutically acceptable salts thereof.

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65. The composition of Claim 63 in an intravenous dosage form.